REMARKS

Entry of the foregoing, re-examination and reconsideration of the subject matter identified in caption, as amended, pursuant to and consistent with 37 C.F.R. § 1.111, and in light of the remarks which follow, are respectfully requested.

The specification has been amended at pages 4, 7, 37, 209, 254 and 255 to show the trademarks in capital letters.

Claims 1-3 have been amended to recite proper Markush language and have replaced "and where" with "or". Claim 4 has been amended to replace "and" with "or" and to delete a space and a comma. Claim 15 has been amended to add the word "or" to recite proper claim language. Such amendments do not narrow the scope of the claims.

Claims 14, 32, 35 and 39-91 have been cancelled. Upon entry of the Amendment, claims 1-13, 15-31, 33, 34 and 36-38 will be pending in the application.

Applicants note with appreciation that claim 13 is allowed.

I. Response to Objection to the Specification

The specification was objected to for the informalities as set forth in paragraph 4 of the Office Action.

In response thereto, Applicants have amended the specification to capitalize the objected-to trademarks. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the objection.

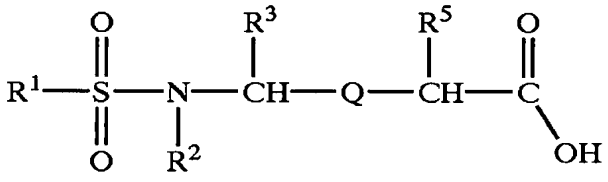
II. Response to Rejection under 35 U.S.C. § 103(a)

Claims 1-12, 15-31, 33, 34 and 36-38 were rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 6,489,300 to Thorsett et al. in view of U.S. Application Publication No. 2002/0161006 to Kawamura et al. for the reasons set forth at pages 4-5 of the Office Action.

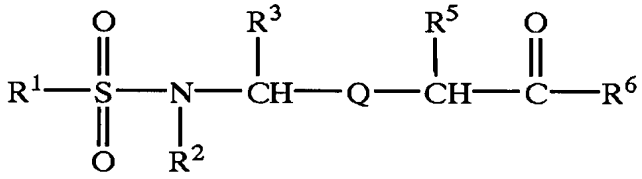
Applicants respectfully submit these claims are not obvious over Thorsett in view of Kawamura et al. and these claims are allowable.

To establish a *prima facie* case of obviousness, three basic criteria must be met. (MPEP 2143) First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Thorsett et al. disclose a specific family of compounds that bind VLA-4. The compounds of Thorsett el al. have structural formulas 1 and 1A:



(I)



(IA)

where R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 form a heterocyclic or a substituted heterocyclic group.

Thorsett et al. disclose that the compounds are useful in inhibiting leukocyte adhesion. Thorsett et al. teach that "reduction in motor impairment is based on blocking adhesion between leukocytes and the endothelium and correlates with anti-inflammatory activity in the candidate compounds." [col. 187, lines 28-31] Thorstett et al. also teach:

> In other organ systems, tissue damage also occurs via an adhesion mechanism resulting in migration or activation of leukocytes. For example, it has been shown that the initial insult following myocardial ischemia to heart tissue can be further complicated by leukocyte entry to the injured tissue causing still further insult (Vedder et al.[5]). Other inflammatory conditions mediated by an adhesion mechanism include, by way of example, asthma[6-8], Alzheimer's disease, atherosclerosis[9-10], AIDS dementia[11], diabetes[12-14] (including acute juvenile onset diabetes), inflammatory bowel disease[15] (including ulcerative colitis and Crohn's disease), multiple sclerosis[16-17], rheumatoid arthritis[18-21], tissue transplantation[22], tumor metastasis[23-28], meningitis, encephalitis, stroke, and other cerebral traumas, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury such as that which occurs in adult respiratory distress syndrome. (column 2, lines 45-62) (Emphasis added by Applicants)

Thorsett et al. does not mention any affect on myelinization, nor do they mention or teach the use of the compounds to promote myelinization of nerve cells. Remyelinization of nerve cells using the specific claimed compounds is the Applicants' invention. This is a new previously unknown use of the claimed compounds. It is well established that new uses of known compounds are patentable.

Kawamura et al. teach a composition comprising specific 1,4-dihydropyridine compounds that are antagonists of bradykinin ("BK") useful in the treatment of inflammation and a variety of conditions in which inflammation is a component of the condition. The Examiner has alleged that Kawamura et al. teach a composition comprising prednisolone and

adhesion molecule inhibitors, e.g. VLA-4 antagonist can be used for treating multiple sclerosis via parental administration in humans and cites page 1, paragraph [0001]; page 9, paragraph [0164]; page 12, paragraph [0200]; and page 23, paragraph [0305]. Applicants respectfully submit that the Examiner has not correctly characterized the teachings of Kawamura et al. The first two paragraphs, [0001] and [0164], cited by the Examiner teach that the 1,4-dihydropyridine compounds of their invention can be used for the treatment of multiple sclerosis. These paragraphs do not teach that any adhesion molecule inhibitor can be used. Paragraph [0200] states:

> The present invention still further relates to the combination of a compound of formula (I) together with one or more members selected from the group consisting of the following: ... (cc) adhesion molecule inhibitors including VLA-4 antagonists; ... (s) inhaled glucocorticoids with reduced systemic side effects, including prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, and mometasone furoate;

Kawamura et al. teach that a 1,4-dihydropyridine can be combined with an adhesion molecule inhibitor and prednisolone, but this is different than indicating that an adhesion molecule inhibitor and prednisolone can be used for the treatment of multiple sclerosis. Finally, paragraph [0305] indicates that "For parenteral administration, solutions of a compound of the present invention [1,4-dihydropyridine compounds] in either sesame or peanut oil or in aqueous propylene glycol may be employed." Thus Kawamura et al. does not teach a composition comprising prednisolone and adhesion molecule inhibitors, e.g. VLA-4 antagonist can be used for treating multiple sclerosis via parentral administration.

Claims 1-5, 15 and 22 are the independent claims for which this obviousness rejection was made. These claims are not obvious over the cited prior art because the present invention relates to methods of promoting remyelinization of nerve cells, while the cited prior does not teach or suggest remyelinization. This aspect of the invention is discussed below. For several of the claims, the claimed compounds are distinct, and not obvious, from those of the cited prior art. These will be discussed in a separate section following the section on remyelinization of nerve cells.

Remyelinization of nerve cells

To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. There is no suggestion or motivation in the prior art to combine Thorsett et al. with Kawamura et al. to arrive at a method of promoting remyelinization of nerve cells. Nor has the Examiner alleged any such motivation, as evidenced by page 5, second paragraph of the Office Action, which states:

> "Regarding the method of promoting remyelinization of nerve cells as recited in instant claims 1-38, [end of paragraph]

Applicants' respectfully submit that the Examiner has not provided in the Office Action any reasoning why the method of promoting remyelinization is obvious since this section of the Office Action is blank. Applicants are providing herein a general explanation as to why discovering a method of promoting remyelinization is not obvious, as they cannot respond to any specific points raised by the Examiner, as none were made. Under the circumstances, it would not be proper to make the next rejection of these claims final since

Applicants have not been given the opportunity to address this issue since there are no comments from the Examiner on this issue.

Applicants have indicated in the specification that "none of the current treatment modalities inhibit demyelination, let alone promotes or allows spontaneous remyelination or reduces paralysis." (see page 37, lines 30-31). Applicants have shown in the various Examples in the specification that with the dosing regimens used, receptor saturation levels of the claimed compounds were maintained (see for example page 420, lines 22- page 421 line 3 page 430, lines 16-18) and remyelination occurred. Example 2. Spontaneous Remyelination Following Prolonged Inhibition of α_4 Integrin in Chronic EAE (see page 429) demonstrates that prolonged administration of a compound of the claimed invention "allowed for spontaneous remyelination of the spinal cord of animals with chronic progressive EAE." (page 433, lines 8-12). There is no indication in the cited prior art that treatment with these compounds would promote remyelination. Therefore there is no motivation to combine the cited prior art references to obtain Applicants' invention.

To establish a *prima facie* case of obviousness, there must be a reasonable expectation of success. There is no reasonable expectation of success based on the teachings in Thorsett et al. and Kawamura et al. that the compounds claimed in Applicants' invention would promote remyelinization, especially when both cited references are silent on remyelinization. There cannot be a reasonable expectation of success in inventing a method for promoting remyelinization of nerve cells when neither of the cited prior art teaches, or even mentions, remyelinization of nerve cells. One of ordinary skill in the art would realize that remyelinization of nerve cells does not occur with current therapies. See Dubois-Dalcq et al (Enhancing Central Nervous System Remyelination in Multiple Sclerosis, Neuron. Vol. 48, 9-12, 2005) which teaches

> "While therapies designed to reduce inflammation can decrease the disease burden, they do not directly address the question of myelin repair in chronic disease. Recent advances in the stem cell field, and in particular the biology of adult neural precursor cells, have raised hopes that remyelinating therapies may soon be developed ..."

In addition, Applicants direct the Examiners attention to Foote et al. (Inflammation stimulates remyelination in areas of chronic demyelination, Brain, 128, 528-539)(2005), which teaches that inflammation can stimulate remyelination under certain conditions. Similar observations are found in Hohlfeld (Does inflammation stimulate remyelination?, J. Neurol (2007) 254 [Suppl 1]: 1/47-1/54). Because the prior art teaches that the compounds of the instant application are useful in treating inflammation, and one of ordinary skill in the art would understand that inflammation can stimulate remyelination, there would not be a reasonable expectation of developing a method for promoting remyelination by treating an individual with a compound known to treat inflammation. Therefore there is no reasonable expectation of success in obtaining the methods of Applicants' invention by combining the cited prior art as indicated by the Examiner.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Neither Thorsett nor Kawamura et al. disclose the use of the claimed compounds to promote remyelinization of nerve cells. In addition, as is shown below, the compounds of independent claims 3, 4 and 15, and the claims that depend from claims 3, 4 and 15, are different from those disclosed by Thorsett et al. Therefore, the prior art references, either alone or combined do not teach or suggest all the claim limitations.

Applicants respectfully submit that the claims are not obvious over Thorsett in view of Kawamura et al. and the rejection should be withdrawn.

Differences in Claimed Compounds

The claims of the instant application have definitions of several variables that are distinct from the definition of the corresponding variables in claims of U.S. Patent No. 6,489,300. Claims 1-12, 15-31, 33, 34 and 36-38 of the instant application were rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 6,489,300. Claims 1-5, 15 and 22 are the dependent claims in this rejection.

Claims 1 and 2

The definition of R^2 and R^3 in claims 1 and 2 of the instant application recite:

> R^2 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and R^1 and R^2 together with the nitrogen atom bound to R^2 and the SO_2 group bound to R^1 can form a heterocyclic or a substituted heterocyclic group;
>
> R^3 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and, when R^2 does not form a heterocyclic group with R^1, R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 can form a heterocyclic or a substituted heterocyclic group;

The definitions of R^2 and R^3 in US 6,489,300 recite:

> R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 form a heterocyclic or a substituted heterocyclic group

Therefore the compounds of claims 1 and 2 of the instant application are structurally distinct from the compounds in US 6,489,300.

Claims 3 and 4

The structures of the compounds of claims 3 and 4 differ from the structure of the compounds in US 6,489,300 in two ways.

First, the definition of R^{22} and R^{23} in claims 3 and 4 of the instant application, which correspond to R^2 and R^3 in U.S. Patent No. 6,489,300, recites:

R^{22} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and R^{21} and R^{22} together with the nitrogen atom bound to R^{22} and the SO_2 group bound to R^{21} can form a heterocyclic or a substituted heterocyclic group;

R^{23} is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, substituted heterocyclic and where R^{22} and R^{23} together with the nitrogen atom bound to R^{22} and the carbon atom bound to R^{23} can form a saturated heterocyclic group or a saturated substituted heterocyclic group with the proviso that when monosubstituted, the substituent on said saturated substituted heterocyclic group is not carboxyl.

The definitions of R^2 and R^3 in US 6,489,300 recite:

R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 form a heterocyclic or a substituted heterocyclic group

Therefore the compounds of claims 3 and 4 of the instant application are structurally distinct from the compounds in US 6,489,300.

Also the definition of R^{25} in claims 3 and 4 of the instant application is different than the definition of R^5 in U.S. Patent No. 6,489,300. The definition of R^{25} as recited in claims 3 and 4 is:

R^{25} is $-CH_2Ar^{22}-R^{25'}$ where Ar^{22} is aryl or heteroaryl and $R^{25'}$ is selected from the group consisting of aryl, heteroaryl, substituted aryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, aryloxy, substituted aryloxy, aralkoxy, substituted aralkoxy, heteroaryloxy, substituted heteroaryloxy, heterocyclic-O-, substituted heterocyclic-O-, heteroaralkoxy, and substituted heteroaralkoxy.

The definition of R^5 recited in US 6,489,300 is:

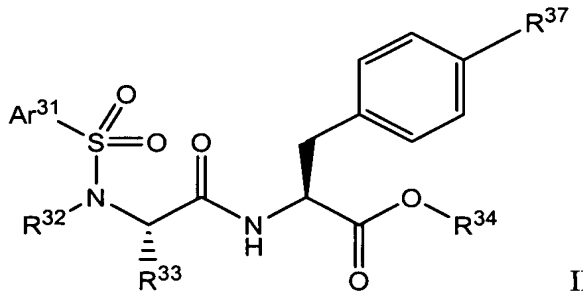
R^5 is $-(CH_2)_x$-Ar-$R^{5'}$ where $R^{5'}$ is selected from the group consisting of -O-Z-NR^8R^8 and -O-Z-R^{12} wherein R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R^8 and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, R^{12} is

selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and -SO_2-.

Therefore the compounds of claims 3 and 4 of the instant application are structurally distinct from the compounds in US 6,489,300.

Claim15

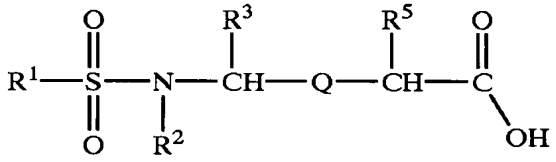
Claim 15 of Applicants' invention recites a compound of formula IIB:



IIB

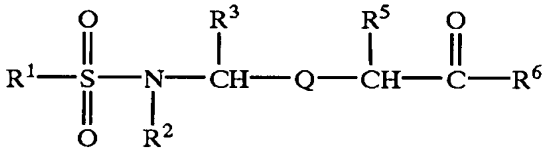
where R^{37} is aryl, heteroaryl, substituted aryl, substituted heteroaryl, heterocyclic, substituted heterocyclic, aryloxy, substituted aryloxy, aralkoxy, substituted aralkoxy, heteroaryloxy, or substituted heteroaryloxy.

The compounds of US 6,489,300 have the following structures:



I

and



IA

The key element that that distinguished the compounds in claim 15 of the present invention from US 6,489,300 is the definition of R^5 in US 6,489,300 which recites:

> R^5 is $-(CH_2)_x$-Ar-$R^{5'}$ where $R^{5'}$ is selected from the group consisting of -O-Z-$NR^8R^{8'}$ and -O-Z-R^{12} wherein R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R^8 and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and $-SO_2-$.

This means that the compounds of US 6,489,300 must have one of the following structures as R^5:

$$-(CH_2)_x\text{-Ar-O-C(O)-}NR^8R^8$$
$$-(CH_2)_x\text{-Ar-O-}SO_2\text{-}NR^8R^8$$
$$-(CH_2)_x\text{-Ar-O-C(O)-}R^{12}$$
$$-(CH_2)_x\text{-Ar-O-}SO_2\text{-}R^{12'}$$

Thus there are four possible groups that can be attached to the Ar group in the compounds of US 6,489,300: -O-C(O)-NR8R8, -O-SO2-NR8R8, -O-C(O)-R12, and -O-SO2-R12.

However none of the allowed R^{37} groups in claim 15 of the instant application is one of the four allowed groups that can be attached to the Ar group in the compounds of US 6,489,3001.

Therefore the compounds of claim 15 of the instant application are structurally distinct from the compounds in US 6,489,300.

Claims 16- 21

Claims 16-21 depend from claim 15. The compounds of claim 15 were shown above to be structurally distinct from the compounds of US 6,489,300. Therefore the compounds in claims 16- 21 are also structurally distinct from the compounds of US 6,489,300.

Applicants respectfully submit that Claims 1-12, 15-31, 33, 34 and 36-38 are not obvious over Thorsett in view of Kawamura et al. for the above mentioned reasons. Applicants therefore request that this rejection be withdrawn.

III. Response to Obviousness-Type Double Patenting Rejection

A. Claims 1-5, 13 and 15 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 10 of U.S. Patent No. 6,291,453; claims 1, 2 and 16 of U.S. Patent No. 6,362,341; claims 1, 2, 15 and 16 of U.S. Patent No. 6,436,904; claims 1 and 11 of U.S. Patent No. 6,492,421; claims 1, 2, 10 and 11 of U.S. Patent No. 6,525,026; claims 1 and 2 of U.S. Patent No. 6,559,127; claims 1, 2 and 14 of U.S. Patent No. 6,583,139; claims 1, 2 and 11 of U.S. Patent No. 6,586,602; claims 1 and 2 of U.S. Patent No. 6,900,179; claims 1, 2, 9 and 10 of U.S. Patent No. 6,949,570; claims 1, 2 and 10 of U.S. Patent No. 7,030,114; and claims 1, 2 and 9-11 of U.S. Patent No. 7,166,580.

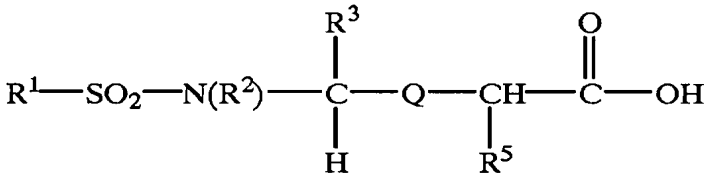
Applicants maintain that an obviousness rejection cannot be maintained against these cited patents for at least two reasons. First, the claims of Applicants' invention are directed towards methods of using specific compounds to promote remyelinization of nerve cells and none of these cited patents teach nor suggest use of the compounds to promote remyelinization of nerve cells. The above discussion of use of the compounds to promote remyelinization of nerve cells also applies to these patents. Additionally, the cited claims of many of the cited patents require compounds that are structurally distinct from the claimed compounds of the instant application. A detailed analysis of these cited claims is given below.

U.S. 6,291,453 - claims 1 and 10

The difference between the structures in the instant application and the structures in claims 1 and 10 of US 6,291,453 is different definitions of R^5.

1. A compound of formula I:

I



wherein:
R^5 is $-(CH_2)_x$ -Ar-$R^{5'}$ where $R^{5'}$ is selected from the group consisting of $-NR^{12}C(Z)NR^8R^{8'}$ and $-NR^{12}C(Z)R^{13}$ wherein R^{12} is selected from the group consisting of hydrogen, alkyl and aryl, R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, heteroaryl and substituted heteroaryl provided that when Z is oxygen, at least one of R^8 and $R^{8'}$ is substituted alkyl, cycloalkyl, substituted cycloalkyl, saturated heterocyclic other than morpholino and thiomorpholino, or substituted heterocyclic, and R^8 and $R^{8'}$ can be joined to form a saturated heterocycle other than morpholino or thiomorpholino, a saturated substituted heterocycle or a saturated/unsaturated heterocycle having an amino group substituted with an alkoxycarbonyl substituent, and further provided that when Z is sulfur, at least one of R^8 and $R^{8'}$ is a group other than aryl, substituted aryl, heteroaryl or substituted heteroaryl, R^{13} is selected from the group consisting of saturated heterocycle other than morpholino and thiomorpholino, and substituted heterocycle, and Z is selected from the group consisting of oxygen, sulfur and NR^{12} where R^{12} is as defined above,

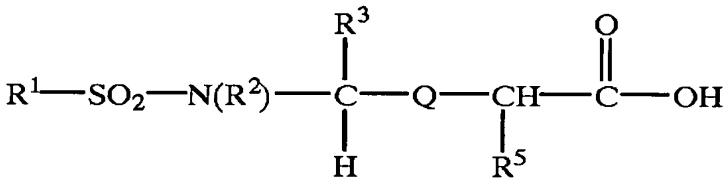
10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula I: etc. as in claim 1.

U.S. 6,362,341 - claims 1, 2 and 16

There are two differences between the structures in the instant application and the structures of the compound in claims 1, 2 and 16 of US 6,362,341. The differences are in the definitions of "R^2 and R^3" and R^5.

1. A compound of formula I:

I



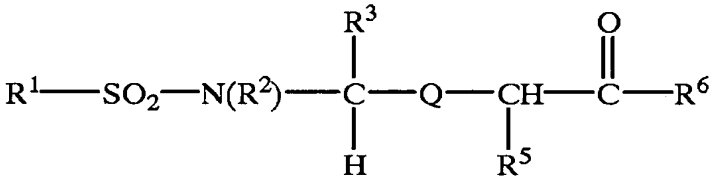
wherein:

R^2 and R^3, together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3, form a saturated heterocyclic group or a saturated substituted heterocyclic group with the proviso that when monosubstituted, the substituent on said saturated heterocyclic group is not carboxyl;

R^5 is selected from the group consisting of $-(CH_2)_n$-aryl and $-(CH_2)_n$-heteroaryl, where n is an integer equal to 1 to 4;

2. A compound of formula II:

II



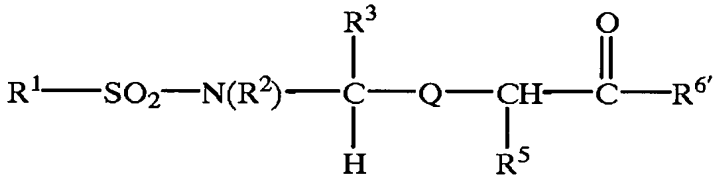
wherein:

R^2 and R^3, together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3, form a saturated heterocyclic group or a saturated substituted heterocyclic group with the proviso that when monosubstituted, the substituent on said saturated heterocyclic group is not carboxyl;

R^5 is selected from the group consisting of $-(CH_2)_n$-aryl and $-(CH_2)_n$-heteroaryl, where n is an integer equal to 1 to 4;

16. A compound of formula III:

III



wherein:

R^2 and R^3, together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3, form a saturated heterocyclic group or a saturated substituted heterocyclic group wherein said saturated heterocyclic group or a saturated substituted heterocyclic group is selected to form a thiazolin-4-yl group, with the proviso that when monosubstituted, the substituent on said saturated heterocyclic group is not carboxyl;

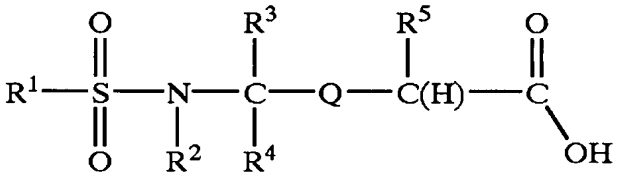
R^5 is selected from the group consisting of $-(CH_2)_n$-aryl and $-(CH_2)_n$-heteroaryl, where n is an integer equal to 1 to 4;

U.S. 6,436,904- claims 1, 2, 15 and 16

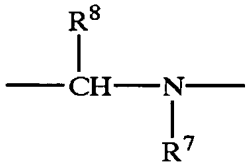
The difference between the structures in the instant application and the structures in claims 1, 2, 15 and 16 of US 6,436,904 is the definition of Q.

1. A compound of formula I:

I



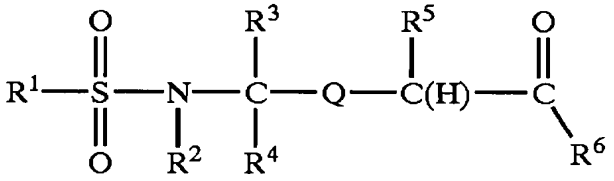
Q is



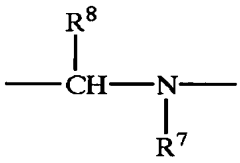
wherein R^7 is selected from the group consisting of hydrogen, alkyl and substituted alkyl; R^8 is selected from the group consisting of hydrogen, alkyl and substituted alkyl; or R^7 arid R^8 together with the nitrogen atom bound to R^7 and the carbon bound to R^8 can form a heterocyclic or substituted heterocyclic ring.

2. A compound of formula IA:

IA



Q is



wherein R^7 is selected from the group consisting of hydrogen, alkyl and substituted alkyl; R^8 is selected from the group consisting of hydrogen, alkyl and substituted alkyl; or R^7 and R^8 together with the nitrogen atom bound to R^7 and the carbon bound to R^8 can form a heterocyclic or substituted heterocyclic ring;

15. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula I: where formula I is defined as in claim 1.

16. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula IA: where formula IA is defined as in claim 2.

U.S. 6,492,421 - claims 1 and 11

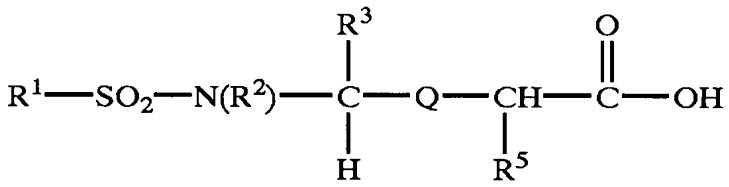
The definition of R^5, which covers approximately 5 columns of specific elements, does not include the definition of R^5 in the current application.

U.S. 6,559,127- claims 1 and 2

The difference between the structures in the instant application and the structures in claims 1 and 2 of US 6,559,127 is that the provisios of claims 1 and 2 of US 6,559,127 remove the compounds of the current application.

1. A compound of formula 1:

I

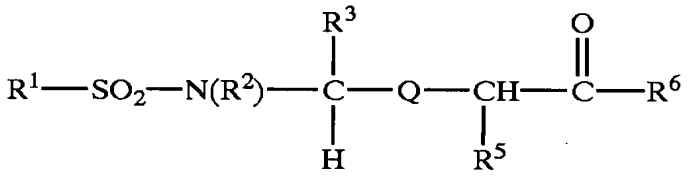


With the proviso that:

A. R^5 is not $-(CH_2)_x$-Ar-$R^{5'}$ where $^{R''}$ is selected from the group consisting of -O-Z-$NR^8R^{8'}$ and -O-Z-R^{12} wherein R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R^8 and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and -SO_2-,

2. A compound of formula 1A:

IA



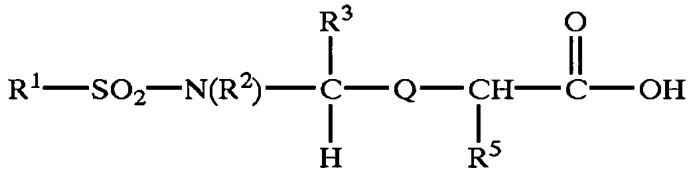
With same proviso as in claim 1.

U.S. 6,583,139- claims 1, 2 and 14

The difference between the structures in the instant application and the structures in claims 1, 2 and 14 of US 6,583,139 is that the provisios of claims 1 and 2 of US 6,583,139 remove the compounds of the current application. Claim 14 depends from claims 1 and 2.

1. A compound of formula 1:

I

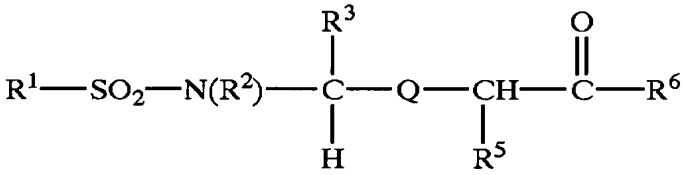


With the further provisos that:

B. R5 is not -(CH2)$_x$-Ar-R$^{5'}$ where R$^{5'}$ is -O-Z-NR^{30}R$^{30'}$ or -O--Z-R^{12}, wherein R^{30} and R$^{30'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R.sup.30 and R.sup.30' are joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycles and substituted heterocycles, and Z is selected from the group consisting of -C(O)- and -SO^2 -,

2. A compound of formula 1A:

IA



With same proviso as in claim 1.

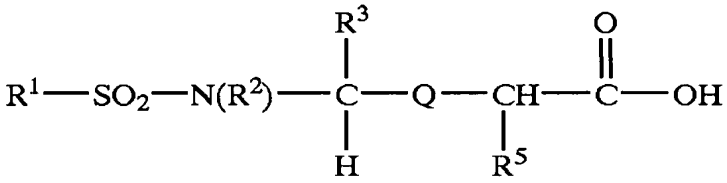
14. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of one or more compounds of claim 1 or 2.

U.S. 6,586,602 – claims 1, 2 and 11

The difference between the structures in the instant application and the structures in claims 1, 2 and 11 of US 6,586,602 is the definition of R^2 and R^3. Claim 11 depends from claims 1 and 2.

1. A compound of formula 1:

I

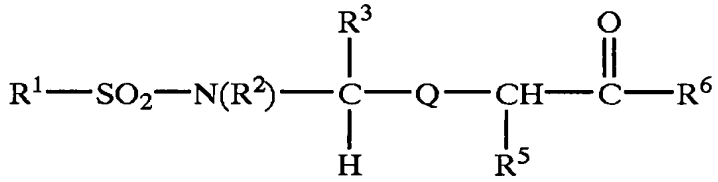


where

R^2 and R^3, together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 form a saturated heterocyclic group or a saturated substituted heterocyclic group with the proviso that when monosubstituted, the substituent on said saturated heterocyclic group is not carboxyl;

2. A compound of formula 1A:

II



With the same definition of R^2 and R^3 as in claim 1

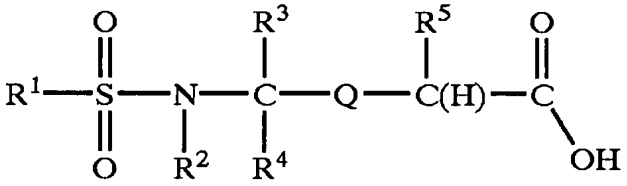
11. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of one or more of the compounds of claims 1 or 2.

U.S. 6,949,570- claims 1, 2, 9 and 10

The difference between the structures in the instant application and the structures in claims 1 and 2 of US 6,949,570 is the definition of Q. In the instant application Q is $-C(X)NR^7-$ wherein R^7 is selected from the group consisting of hydrogen and alkyl; and X is selected from the group consisting of oxygen and sulfur. Claims 9 and 10 of US 6,949570 depend from claims 1 and 2.

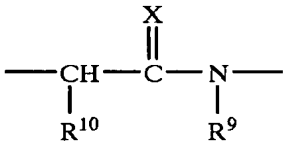
1. A compound of formula 1:

I



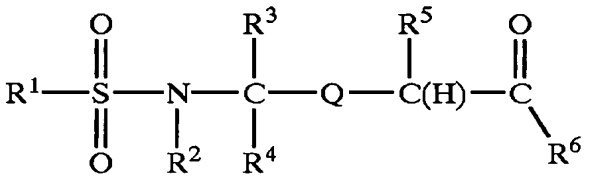
wherein

Q is



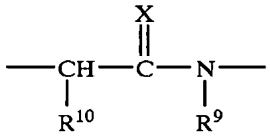
2. A compound of formula 1A:

IA



wherein

Q is



9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula I:

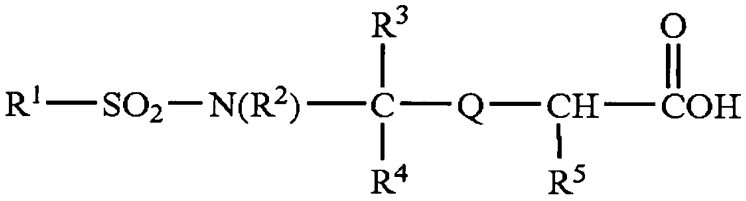
10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula IA:

U.S. 7,030,114 – claims 1, 2 and 10

The difference between the structures in the instant application and the structures in claims 1, 2 and 10 of US 7,030,114 is the definition of R^2 and R^3.

1. A compound of formula 1:

I



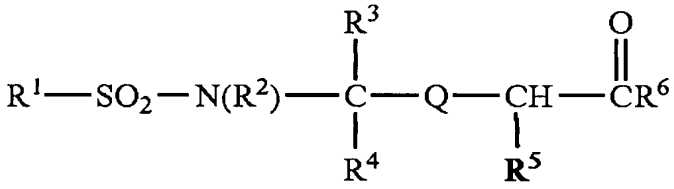
where

R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 form a heterocyclic or a substituted heterocyclic group selected from the group

consisting of thiazolidinyl, piperidinyl and pyrrolidinyl wherein said substituted heterocyclic group consists of from 1 to 2 substituents selected from the group consisting of fluoro, methyl, hydroxyl, amino, phenyl, thiophenyl and thiobenyl

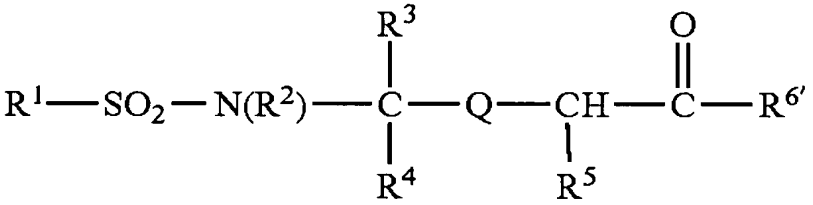
2. A compound of formula 1A:

IA



With the same definition of R^2 and R^3 as in claim 1.

10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of the formula:



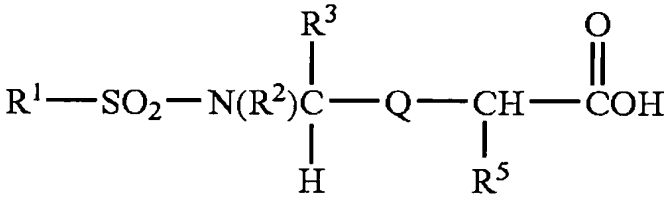
with the same definition of R^2 and R^3 as in claim 1.

U.S. 7,166,580 - claims 1, 2 and 9-11

The difference between the structures in the instant application and the structures in claims 1, 2 and 9-11 of US 7,166,580 is that the provisio of claims 1, 2, 10 and 11 of US 7,166,580 remove the compounds of the current application. Claim 9 depends from claims 1 and 2.

1. The compound of formula I:

I

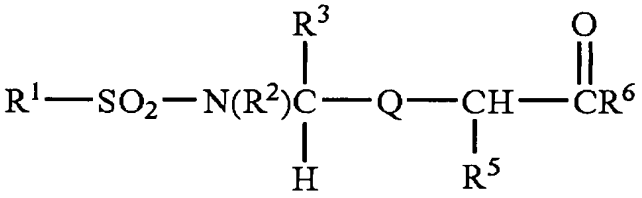


with the further provisos that:

A. R^5 not $-(CH_2)_x$-Ar-R_5 where $R^{5'}$ is selected from the group consisting of -O-Z-$NR^8R^{8'}$ and -O-Z-R^{12} wherein R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R^8 and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and $-SO_2$-,

2. The compound of formula II:

II



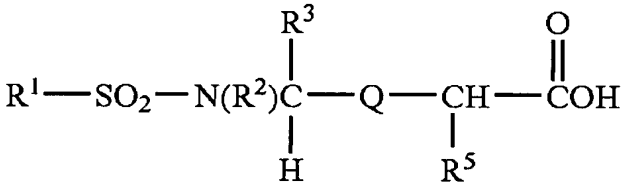
with the further provisos that:

A. R^5 not $-(CH_2)_x$-Ar-R_5 where $R^{5'}$ is selected from the group consisting of -O-Z-$NR^8R^{8'}$ and -O-Z-R^{12} wherein R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R^8 and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and -SO_2-,

9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an amount of one or more of the compounds of any of claims 1, 2 or 8 wherein the compound is effective to block or inhibit cellular adhesion associated with a disease.

10. The compound of formula I:

I

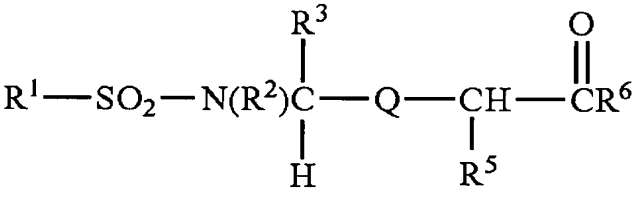


with the further provisos that:

A. R^5 not $-(CH_2)_x$-Ar-R_5 where $R^{5'}$ is selected from the group consisting of -O-Z-$NR^8R^{8'}$ and -O-Z-R^{12} wherein R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R^8 and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and -SO_2-,

11. The compound of formula II:

II



with the further provisos that:

A. R^5 not $-(CH_2)_x$-Ar-R_5 where $R^{5'}$ is selected from the group consisting of -O-Z-$NR^8R^{8'}$ and -O-Z-R^{12} wherein R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R^8 and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and $-SO_2-$,

If the arguments presented above are not successful, Applicants will file a Terminal Disclaimer for any of the following patents, as required: U.S. Patent Nos. 6,291,453; 6,436,904; 6,492,421; 6,559,127; 6,949,570; 7,030,114; and 7,166,580, which are assigned to Elan Pharmaceuticals, and to U.S. Patent Nos. 6,362,341, 6,525,026, US 6,583,139 and 6,900,179, which are co-assigned to Elan Pharmaceuticals and Wyeth as a result of a joint research agreement between the two co-assignees. US 6,586,602 does not appear to be currently assigned but the assignment will be recorded and if necessary, a Terminal Disclaimer will be filed.

B. Claims 1-5, 13 and 15 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 19-21 of Ashwell et al. (US 6,291,453), claims 11 and 13 of Thorsett et al. (US 6,362,341), claims 28 and 29 of Ashwell et al. (US 6,436,904), claims 22, 34 and 35 of Thorsett et al. (US 6,492,421). claim 18 of Thorsett et al. (US 6,525,026), claim 9 of Dappen et al. (US 6,559,127), claims 13 and 15 of Thorsett et al. (US 6,583,139); claims 10 and 12 of Thorsett et al. (US 6,586,602), claim 13 of Thorsett et al. (US 6,900,179) and claims 11 and 12 of Thorsett et al. (US 7,030,114) in view of Thorsett et al. (US 6,489,300).

Applicants maintain that an obviousness rejection cannot be maintained against these cited patents for at least two reasons. First, the claims of Applicants' invention are directed

towards methods of using specific compounds to promote remyelinization of nerve cells and none of these cited patents teach nor suggest use of the compounds to promote remyelinization of nerve cells. The above discussion of use of the compounds to promote remyelinization of nerve cells also applies to these patents. Additionally, the cited claims of many of the cited patents require compounds that are structurally distinct from the claimed compounds of the instant application. A detailed analysis of these cited claims is given below.

U.S. 6,291,453 - claims19-21

Claim 19 depends from claim 1. It was shown above that the definition of R^5 in claim 1 of US 6,291,453 is different than the definition of R^5 in the current application. Claims 20 and 21 depend from claim 10, which is directed towards pharmaceutical compositions comprising the compounds of claim 1.

19. A method for binding VLA-4 in a biological sample which method comprises contacting the biological sample with a compound of claim 1 conditions wherein said compound binds to VLA-4.

20. A method for treating an inflammatory condition in a mammalian patient which condition is mediated by VLA-4 which method comprises administering to said patient a therapeutically effective amount of the pharmaceutical composition of claim 10.

21. A method for treating diseases mediated by VLA-4 which method comprises administering to a mammalian patient a therapeutically effective amount of the pharmaceutical composition of claim 10 wherein the diseases are selected from the group consisting of asthma, atherosclerosis, diabetes, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, tissue transplantation, tumor metastasis, meningitis, encephalitis, stroke, nephritis, retinitis, atopic dermatitis, psoriasis, myocardial ischemia and acute leukocyte-mediated lung injury.

U.S. 6,362,341- claims 11 and 13

Claim 11 depends from claims 1 and 2. It was shown above that there are two structural differences between the compounds in claims 1 and 2 of US 6,362,341 and the claims in the current application. The differences are due to the definitions of: (1) "R^2 and R^3" and (2) R^5. Claim 13 depends from claim 12, which is directed towards pharmaceutical compositions comprising the compounds of claims 1 or 2.

11. A method for binding VLA-4 in a biological sample which method comprises contacting the biological sample with a compound according to claim 1 or 2 under conditions wherein said compound binds to VLA-4.

13. A method for the treatment of an inflammatory disease in a patient mediated by VLA-4 which method comprises administering to the patient the pharmaceutical composition of claim 12.

U.S. 6,436,904- claims 28 and 29

Claim 28 depends from claims 1 and 2. It was shown above that the definition of Q in claims 1 and 2 of US 6,436,904 is different than the definition of Q in the current application. Claims 28 and 29 depend from claims 15 and 16, which are directed towards pharmaceutical compositions comprising the compounds that are claimed as having the same definition of Q as described in claims 1 and 2.

28. A method for binding VLA-4 in a biological sample which method comprises contacting the biological sample with a compound of claim 1 or 2 under conditions wherein said compound binds to VLA-4.

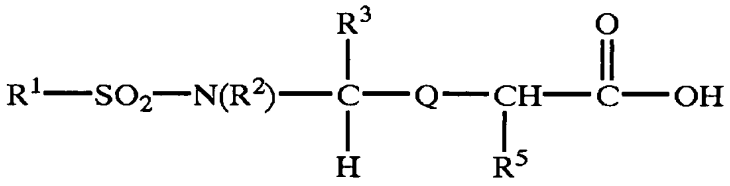
29. A method for treating an inflammatory condition in a mammalian patient which condition is mediated by VLA-4 which method comprises administering to said patient a therapeutically effective amount of a pharmaceutical composition of claim 15 or 16.

U.S. 6,559,127- claim 9

The provisios of claims 1 and 2 remove the compounds of the current application.

1. A compound of formula 1:

I

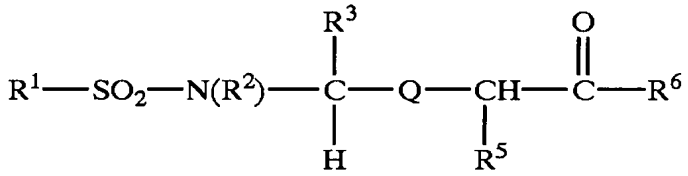


With the proviso that:

A. R^5 is not $-(CH_2)_x$-Ar-$R^{5'}$ where $^{R''}$ is selected from the group consisting of -O-Z-$NR^8R^{8'}$ and -O-Z-R^{12} wherein R^8 and $R^{8'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R^8 and $R^{8'}$ are joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycle and substituted heterocycle, and Z is selected from the group consisting of -C(O)- and -SO_2-,

2. A compound of formula 1A:

IA



With same proviso as in claim 1.

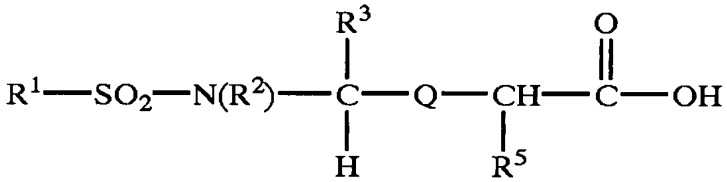
9. A method for binding a compound according to claim 1 or claim 2 to very late antigen-4 that is present in a biological sample, said method comprising contacting the biological sample with a compound according to claim 1 or claim 2 for a time and under conditions effective to achieve binding between very late anitigen-4 and said compound.

U.S. 6,583,139- claims 13 and 15

The provisios of claims 1 and 2 remove the compounds of the current application. Claims 13-15 depend from claims 1 and 2.

1. A compound of formula 1:

I

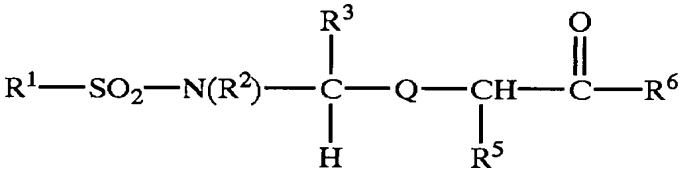


With the further provisos that:

B. R5 is not -$(CH2)_x$-Ar-$R^{5'}$ where $R^{5'}$ is -O-Z-$NR^{30}R^{30'}$ or -O--Z-R^{12}, wherein R^{30} and $R^{30'}$ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, and where R.sup.30 and R.sup.30' are joined to form a heterocycle or a substituted heterocycle, R^{12} is selected from the group consisting of heterocycles and substituted heterocycles, and Z is selected from the group consisting of -C(O)- and -SO^2 -,

2. A compound of formula 1A:

IA



With same proviso as in claim 1.

13. A method for binding Very Late Antigen 4 in a biological sample which method comprises contacting the biological sample with a compound of claims 1 or 2 under conditions wherein said compound binds to Very Late Antigen 4.

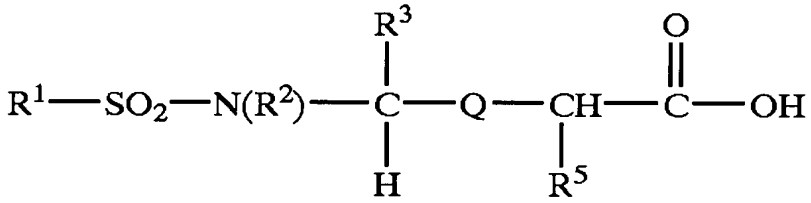
15. A method for treating an inflammatory disease in a mammalian patient which disease is mediated by Very Late Antigen 4 which method comprises administering to said patient a therapeutically effective amount of the pharmaceutical composition of claim 14.

U.S. 6,586,602 – claims 10 and 12

Claims 1 and 2 have a different definition of R^2 and R^3 than the definition of these variables in the instant application. Claim 11 depends from claims 1 and 2.

1. A compound of formula 1:

I

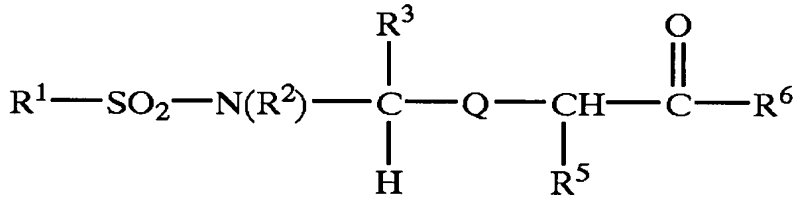


where

R^2 and R^3, together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 form a saturated heterocyclic group or a saturated substituted heterocyclic group with the proviso that when monosubstituted, the substituent on said saturated heterocyclic group is not carboxyl;

2. A compound of formula 1A:

II



With the same definition of R^2 and R^3 as in claim 1

10. A method for binding VLA-4 in a biological sample which method comprises contacting the biological sample with a compound according to claim 1 or 2 under conditions wherein said compound binds to VLA-4.

11. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of one or more of the compounds of claims 1 or 2.

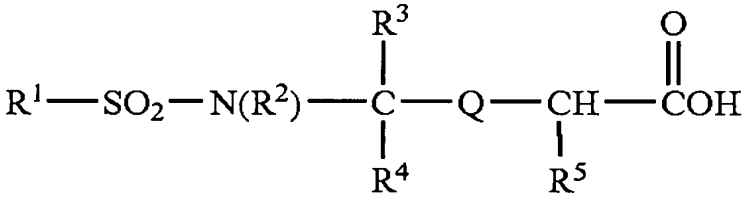
12. A method for the treatment of an inflammatory disease in a patient mediated by VLA-4 which method comprises administering to the patient the pharmaceutical composition of claim 11.

U.S. 7,030,114 – claims 11 and 12

Claims 1, 2 and 10 have a different definition of R^2 and R^3 than the definition of these variables in the instant application.

1. A compound of formula 1:

I

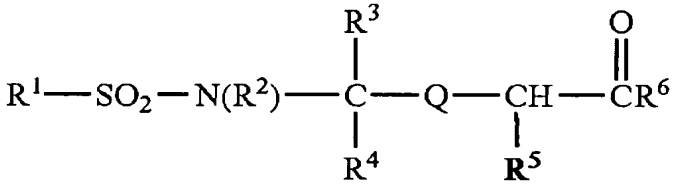


where

R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 form a heterocyclic or a substituted heterocyclic group selected from the group consisting of thiazolidinyl, piperidinyl and pyrrolidinyl wherein said substituted heterocyclic group consists of from 1 to 2 substituents selected from the group consisting of fluoro, methyl, hydroxyl, amino, phenyl, thiophenyl and thiobenyl

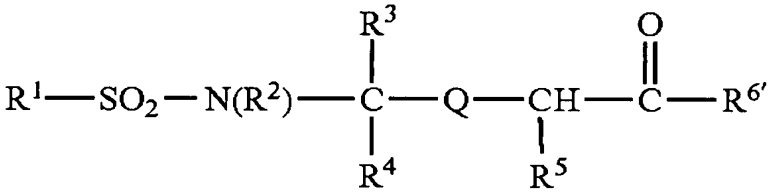
2. A compound of formula 1A:

IA



With the same definition of R^2 and R^3 as in claim 1.

10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of the formula:



with the same definition of R^2 and R^3 as in claim 1.

11. A method for binding VLA-4 in a biological sample which method comprises contacting the biological sample with a compound of claims 1 or 2 under conditions wherein said compound binds to VLA-4.

12. A method for the treatment of an inflammatory disease in a patient mediated by VLA-4 which methods comprise administering to the patient the pharmaceutical composition of claim 10.

If the arguments presented above are not successful, Applicants will file a Terminal Disclaimer for any of the following patents, as required: US 6,291,453; US 6,436,904; US 6,492,421; US 6,559,127 and US 7,030,114, which are assigned to Elan Pharmaceuticals and to US 6,362,341; US 6,525,026; US 6,583,139; US 6,900,179 and U.S. 6,489,300, which are co-assigned to Elan Pharmaceuticals and Wyeth as a result of a joint research agreement between the two co-assignees. US 6,586,602 does not appear to be currently assigned but the assignment will be recorded and if necessary, a Terminal Disclaimer will be filed.

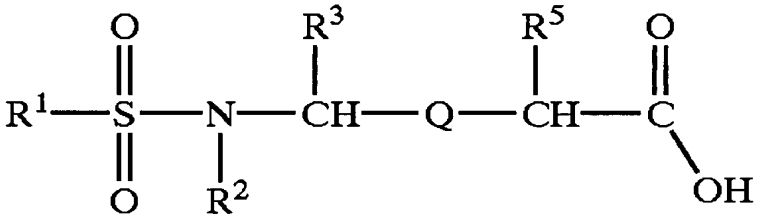
C. Claims 1-5, 13 and 15 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4 and 7 of Yednock et al. (U.S. 6,939, 855) in view of Thorsett et al. (U.S. 6,489,300).

Applicants maintain that an obviousness rejection cannot be maintained against these cited patents for at least two reasons. First, the claims of Applicants' invention are directed towards methods of using specific compounds to promote remyelinization of nerve cells and neither of these cited patents teach nor suggest use of the compounds to promote remyelinization of nerve cells. The above discussion of use of the compounds to promote remyelinization of nerve cells also applies to these patents. Additionally, the compounds of Thorsett et al. (U.S. 6,489,300) are structurally distinct from the claimed compounds of the instant application. A detailed analysis of the claims of Thorsett et al. is given below.

U.S. 6,489,300

Claims 1 and 2 have a different definition of R^2 and R^3 than the definition of these variables in the instant application

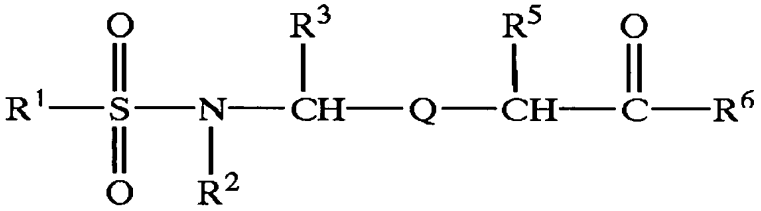
1. A compound of formula 1:



Wherein
R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 form a heterocyclic or a substituted heterocyclic group;

2. A compound of formula 1A:

IA



With the same definition of R^2 and R^3 as in claim 1

If the arguments presented above are not successful, Applicants will file a Terminal Disclaimer for patent U.S. 6,939, 855 which is co-assigned to Elan Pharmaceuticals and Wyeth as a result of a joint research agreement between the two co-assignees.

D. Claims 1-5, 13 and 15 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2 and 12 of Thorsett et al. (U.S. 6,489,300).

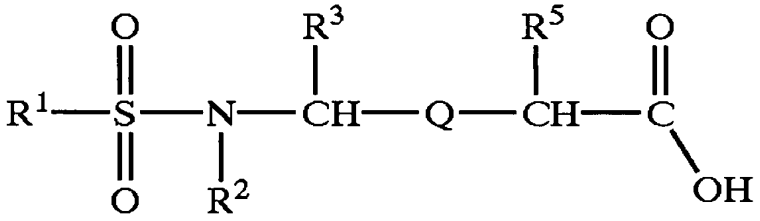
Applicants maintain that an obviousness rejection cannot be maintained against these cited patents for at least two reasons. First, the claims of Applicants' invention are directed towards methods of using specific compounds to promote remyelinization of nerve cells and

none of these cited patents teach nor suggest use of the compounds to promote remyelinization of nerve cells. The above discussion of use of the compounds to promote remyelinization of nerve cells also applies to these patents. Additionally, the cited claims of many of the cited patents require compounds that are structurally distinct from the claimed compounds of the instant application. A detailed analysis of these cited claims is given below.

U.S. 6,489,300 - claims 1, 2 and 12

Claims 1 and 2 have a different definition of R^2 and R^3 than the definition of these variables in the instant application

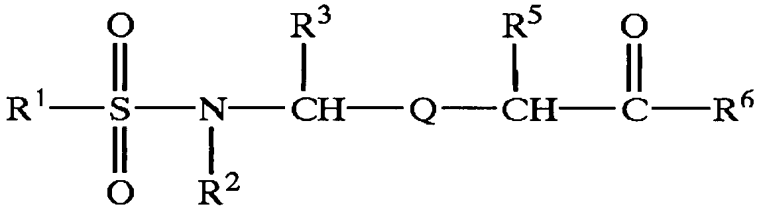
1. A compound of formula 1:



Wherein
R^2 and R^3 together with the nitrogen atom bound to R^2 and the carbon atom bound to R^3 form a heterocyclic or a substituted heterocyclic group;

2. A compound of formula 1A:

IA



With the same definition of R^2 and R^3 as in claim 1

If the arguments presented above regarding the non-obviousness of a method for promoting remyelinization of nerve cells are not successful, Applicants will file a Terminal

Disclaimer for patent U.S. 6,489,300, which is co-assigned to Elan Pharmaceuticals and Wyeth as a result of a joint research agreement between the two co-assignees.

E. Claims 1-5, 13 and 15 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 14 and 17 of copending application Thorsett et al. (US 2003/0065185) and claims 35 and 36 of copending application Thorsett et al. (US 2005/0222119).

The scope of the claims in neither this application nor the copending applications have yet been settled, so it would be premature at this time to file a terminal disclaimer. It is respectfully requested that the Examiner hold this provisional rejection in abeyance until the scope of the claims to otherwise allowable subject matter has been determined.

F. Claims 1-5, 13 and 15 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 22 of copending application Yednock et al. (US 2005/0272668) in view of Thorsett et al. (US 6,489,300) and Yednock et al. (US 6,939,855).

The scope of the claims in neither this nor the copending application has yet been settled, so it would be premature at this time to file a terminal disclaimer. It is respectfully requested that the Examiner hold this provisional rejection in abeyance until the scope of the claims to otherwise allowable subject matter has been determined.

G. Claims 1-5, 13 and 15 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13 and 16

of copending application Thorsett et al. (US 2003/0065185) in view of Thorsett et al. (US 6,489,300).

The scope of the claims in neither this nor the copending application has yet been settled, so it would be premature at this time to file a terminal disclaimer. It is respectfully requested that the Examiner hold this provisional rejection in abeyance until the scope of the claims to otherwise allowable subject matter has been determined.

H. Claims 1-5, 13 and 15 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 35, 36 and 56 of copending application Thorsett et al. (US 2004/0014677) in view of Thorsett et al. (US 6,489,300).

The scope of the claims in neither this nor the copending application has yet been settled, so it would be premature at this time to file a terminal disclaimer. It is respectfully requested that the Examiner hold this provisional rejection in abeyance until the scope of the claims to otherwise allowable subject matter has been determined.

In view of the above, the Examiner is respectfully requested to reconsider and withdraw this provisional nonstatutory obviousness-type double patenting rejection.

IV. Conclusion

Applicants earnestly solicit favorable consideration of the above response and early passage to issue the present application. The Examiner is invited to contact the undersigned at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: November 15, 2007

By: Deborah Yellen Reg No 45904 for
Melissa M. Hayworth
Registration No. 45,774

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620